§119(e) from U.S. Provisional Application Serial Number 60/080,729 (now abandoned) filed April 3, 1998. The entire contents of all the foregoing patent applications are incorporated by reference herein.

REMARKS

Applicants have amended the specification to update the status of related applications. No new matter has been added. Applicants acknowledge the re-numbering of the claims.

Rejection of Claims 22-31 Under 35 U.S.C. §112

Claims 22-31 have been rejected under 35 U.S.C. §112, first paragraph as containing subject matter that was not described in the specification in such a way as to enable one of skill in the art to practice it. According to the office action the "scope of the claimed invention encompasses a genus of antigen specific immune responses that are not described in the specification as filed." It is further stated that "in the instant case, a description of a 'synergistic antigen specific immune response' is a critical element for each species of the claimed invention because a synergistic antigen specific immune response can occur in *any* cell of an organism." It is concluded that the specification "does not provide adequate written description for the broad class of [any and all] synergistic antigen specific immune responses. Therefore, only the embodiments of the invention reduced to practice in the examples meet the written description provision of 35 U.S.C § 112, first paragraph." (Office Action, paper #9, pages 3-4).

There is no basis for the lack of written description rejection. The rejection is based on several general statements to the effect that the specification does not provide guidance to one of skill in the art or a description or definition of a "synergistic antigen specific immune response". The ability of CpG in combination with a cytokine to produce a synergistic immune response forms the basis of the whole description of the invention. It is taught in the first paragraph on page 9 of the specification that:

> "Both CpG oligonucleotides and immunopotentiating cytokines have the ability to produce immune responses on their own when administered to a subject. When the combination of the two is administered together, however, the quantity and type of immune response shifts. For instance, when the CpG oligonucleotide and immunopotentiating cytokine are administered in conjunction with an antigen

> using repeat immunizations, as shown in Figure 3, a synergistic induction in antigen specific IgG is observed."

A "synergistic immune response" is defined on page 36, lines 12-15 as:

> "A synergistic amount is that amount which produces an immune response against a specific antigen that is greater than the sum of the individual effects of either the CpG or the cytokine alone."

CpG ODN, cytokines, and antigens are all defined in the specification. In view of these definitions the term "synergistic antigen specific immune response" is clear to one of skill in the art. There is no basis for the assertion that applicants did not posses the claimed invention commensurate to its scope.

Additionally, the reasoning that "a description of a 'synergistic antigen specific immune response' is a critical element for each species of the claimed invention because a synergistic antigen specific immune response can occur in *any* cell of an organism" is scientifically incorrect. Those of skill in the art are familiar with an antigen specific immune response. It is a response occurring in an immune cell caused by exposure of the immune cell to an antigen. It is not a response that occurs in "any cell of an organism". The immune system recognizes antigen and responds appropriately to the antigen by generating an immune response, i.e., production of antibodies, shift in cytokine expression and activation of T-cells. Antigen specific immune responses are well characterized responses occurring in very specific cells of the body.

With respect to the conclusion that "Therefore, only the embodiments of the invention reduced to practice in the examples meet the written description provision of 35 U.S.C § 112, first paragraph", the Examiner is respectfully requested to provide a legal citation in support of this statement. Applicant is not aware that such a standard exists. In fact, it is Applicants understanding that it is not necessary for the specification to include *any* working examples in order to meet the requirements of enablement and written description. It certainly is not required that each embodiment of a claimed invention be reduced to practice in the examples. If the Examiner is aware of such a legal standard she is requested to provide a source in support of such standard.

Claims 22-43 have been rejected under 35 U.S.C. §112, first paragraph as lacking enablement. According to the Office Action, the specification does not provide enablement for compositions or methods for stimulating a synergistic immune response in any subject. It is stated that "Consequently, the examples set forth in the specification do not constitute support for the entire scope of claims 22-43, and, as a result, the entire scope of claims 22-43 could not be supported without undue experimentation."

The reasoning set forth in support of this rejection includes several statements to the effect that the specification does not provide guidance to one of skill in the art and that undue experimentation would be required to practice the invention. Applicants have addressed each of the statements made by the Examiner.

The first reason provided in the Office Action for lack of enablement is that claims 22-43 represent a broad scope because they read "on any subject and any immunostimulatory CpG oligonucleotide, where it is unpredictable to determine biological effects from one organism to another." Weiner et al is cited for the proposition that not all CpG ODN are alike and more needs to be learned about the heterogeneous responses that occur based on host organism, cell subset, or CpG ODN sequence. Additionally, Krieg and Wagner are cited for the proposition that cytokine response to CpG is much greater in mouse cells than with human or monkey cells.

The Examiner's reliance in objecting to the specification and claims upon a purported failure of the specification to enable the use of CpG and cytokine in any organism, is misplaced for at least the following reasons.

The specification provides guidance with respect to the administration of the compounds of the invention to different subjects, including different antigens useful for treating infectious disease and cancer in different animals. Further guidance is provided concerning routes of administration as well as various methods for formulating the compounds for each of the routes.

Methods for delivering cytokines to subjects, for various purposes, including the treatment of cancer, have been described in many publications and patents (see for instance Rock, US Patent No. 5,869,057, column 10, lines 5-56, of record). Methods for delivering CpG

oligonucleotides to a variety of subjects have also been described in the prior art (see for instance Davis, US Patent No. 5,780,448, of record).

Additionally, many studies have been performed in non-human animals and demonstrated the effectiveness of CpG in stimulating an immune response. Rankin R., et al., (CpG-containing oligodeoxynucleotides augment and switch the immune responses of cattle to bovine herpesvirus-1 glycoprotein D., Vaccine 2002 Jul 26;20(23-24):3014-22) attached hereto as Exhibit 1 demonstrates that *in vivo* administration of CpG oligonucleotides significantly reduces viral shedding. As described in the abstract, administration of CpG to calves significantly reduced the duration of virus shedding after intranasal viral challenge.

Another study by Rankin R. et al., (Exhibit 2, CpG motif identification for veterinary and laboratory species demonstrates that sequence recognition is highly conserved, Antisense Nucleic Acid Drug Dev 2001 Oct; 11(5):333-40) examined CpG immunostimulation on cells from seven veterinary and three laboratory species. As described in the paper, CpG motifs consistently induced an immune response in different species of animals. The *in vitro* studies were further verified using *in vivo* analysis in sheep.

The citation of Krieg and Wagner for the proposition that the cytokine response to CpG is greater in mice than humans or primates is taken out of context. The paragraph from which the quote is taken is referring to potential side effects of CpG DNA therapy. The reference actually teaches:

> "In mice, administration of CpG DNA can trigger systemic inflammatory response syndrome (SIRS) upon endotoxin exposure or following sensitization to TNF-α by treatment with D-galactosamine[6]. However, the magnitude of cytokine response to CpG DNA is much greater in mouse cells than with human or monkey cells; and repeated weekly administration of a highly immune stimulatory CpG ODN in monkeys has not caused substantial pathology, even at does of 10 mg kg^{-1}."

The Examiner has cited the quoted paragraph to demonstrate that human cells produce less cytokine than mouse cells in response to CpG and that thus one of skill in the art would not expect that CpG would work in human or monkey cells to produce cytokine. When examined in the context of the full paragraph cited in the reference it is clear that the cited sentence is referring to a lack of toxic effects observed in human and monkey cells in response to the same

treatment that produces toxic effects in mouse cells. The quote does not support the notion that CpG does not induce an adequate cytokine effect in human or monkey cells.

Weiner et al is also cited for the proposition that the direct effects of CpG ODN on T cells is controversial. This statement is irrelevant. The instant claims are not directed to a method for producing a direct effect on T cells.

The Branch reference is cited to illustrate the state of the art of gene therapy and it is stated that methods of targeting nucleic acids like CpG in a subject "fall into the broad area known as gene therapy methods." There is no scientific or legal basis for this. CpG therapy and gene therapy are completely distinct technologies. CpG ODN are short, often stabilized, oligonucleotides that produce an effect on immune cells. Gene therapy involves the administration of a nucleic acid expressing vector to a target cell. The vector must be taken up by the target, the gene must be expressed and functional protein produced for activity. No gene must be expressed or protein produced for CpG to function. In fact, many studies in the literature have demonstrated that the immune cells simply need to be contacted with CpG to produce an immune response.

It is further stated that "the specification fails to teach how the skilled artisan would use IL-3, IL-5 and IL-12 as an inducer of immune response synergism in a subject a combination of a CpG oligonucleotide" and that one would not accept a correlation between the data showing GM-CSF and other cytokines.

The Examiner has stated that the claims are not enabled because one of ordinary skill in the art would not accept on its face the examples disclosed in the specification as being representative or correlative of the subject matter of the full scope of the claim. No evidence has been provided in support of this assertion. In the absence of some reason or evidence why one of ordinary skill in the art would not accept the examples as being representative or correlative of successful treatment as claimed, the rejection is not appropriate.

Finally it is stated that the quantity of experimentation needed to make or use the invention would be great, because the "de novo determination of immunostimulatory CpG oligonucleotides that induce a synergistic immune response" would require undue experimentation. Therefore it would require trial and error or undue experimentation beyond

which is taught in the specification to practice the invention drawn to the immunostimulation using any CpG oligonucleotide.

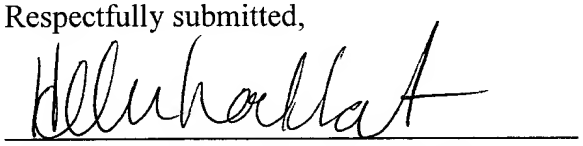
Applicants have provided sufficient guidance to teach one of ordinary skill in the art how to make or obtain the compositions which are useful in the invention and how to deliver those to subjects in order to produce the appropriate immune response. If one of ordinary skill in the art reads the specification and follows the guidelines set forth therein, they will be able to accomplish the methods of the invention, that is, to produce an immune response. For instance, pages 30-35 of the specification describe the different properties of CpG oligonucleotides that are useful for producing an immune response.

Applicants have asserted that combinations of CpG nucleotides and cytokines would produce specific immune effects in a variety of subjects and have provided actual working examples to demonstrate that the invention does work. Applicants have described methods of delivering the compounds including preferred dosages and routes of administration. It is respectfully requested that the rejection be withdrawn.

Summary

Applicants believe that each of the pending claims is in condition for allowance. Applicants respectfully request that the Examiner telephone the undersigned attorney in the event that the claims are not found to be in condition for allowance. If the Examiner has any questions and believes that a telephone conference with the applicants' attorney would prove helpful in expediting the prosecution of this application, the Examiner is urged to call the undersigned at the number listed below.

Respectfully submitted,



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Marked–up Specification

Related Application Information

This application is a continuation [divisional] of U.S. Patent Application Serial Number 09/286,098, filed April 2, 1999, [pending], now issued as US 6,218,371 B1, which claims priority under 35 U.S.C. §119(e) from U.S. Provisional Application Serial Number 60/080,729 (now abandoned) filed April 3, 1998. The entire contents of all the foregoing patent applications are incorporated by reference herein.